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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/644,875

08/21/2003

Ying-Fei Wei

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EXAMINER

ALLEN, MARIANNE P

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/644,875	<b>Applicant(s)</b> WEI ET AL.	
	<b>Examiner</b> Marianne P. Allen	<b>Art Unit</b> 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 10 March 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 25 and 31-44 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 25 and 31-44 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1/30/08</u> .   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/10/08 has been entered.

Applicant's arguments filed 3/10/08 have been fully considered but they are not persuasive.

Claims 25 and 31-44 are under consideration.

### ***Specification***

The amendment filed 6/12/06 remains objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Amendments to page 5, line 3, paragraph [0027] of the specification.

This objection is maintained for reasons of record.

The amendment to page 5 is reproduced below.

[0027] The full-length polypeptide of the present invention as set forth in SEQ ID NO:2 has a putative signal sequence which comprises amino acid 1 through amino acid 45 of SEQ ID

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NO:2 which aids in secretion of the polypeptide from the cell. The polypeptide is further processed wherein amino acid 46 through amino acid ~~214~~ 259 of SEQ ID NO: 2 are cleaved from the polypeptide since this stretch of amino acids is a putative precursor sequence. Further, amino acid ~~264~~ 310 through amino acid 344 represent a putative transmembrane portion which is thought to be necessary to direct the polypeptide to particular target locations for the carrying out of biological functions as herein after described. The transmembrane portion may also be cleaved from the polypeptide such that the putative soluble portion of the polypeptide of the present invention comprises amino acid ~~215~~ 260 through amino acid ~~264~~ 309 of SEQ ID NO:2.

Applicant has altered amino acid end point ranges for different domains of SEQ ID NO: 2 as disclosed on page 5 stating that they are obvious typographical errors. This is not agreed with.

Applicant admits inconsistencies exist in numbering between the specification and sequence listing in PCT/US95/06386, particularly with respect to SEQ ID NO: 2.

The legal standard for obvious errors, based on the MPEP 2163.07(II), is that “An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).” So two elements are necessary to correct the error, (1) the determination that the skilled practitioner would recognize the existence of error and (2) the determination that the skilled practitioner would recognize the appropriate correction.

The cited case, *In re Oda*, states (see page 6, bottom of page to page 7) “Running through the foregoing discussion of the law is the clear and basic concept that *the invention* described in the original patent must not be changed. We note, first of all, that that is not a problem in this case. The invention before us, as defined in the claims, consists of three specific chemical compounds, there is no change proposed in the claims are in the description of the claimed compounds in the specification, there is no deviation whatever with respect to the invention.”

From this discussion it is clear that when the invention (which is the claims) is at issue, it cannot be changed. In particular, the *Oda* court makes it clear that if the chemical compounds in the claims or specification were changed, this would be new matter. In *Oda*, the change was in how to make the chemical compounds and at page 7, it is clear that there were four independent bases to support an identification of the subject matter at issue.

Therefore, applying the first factor from the MPEP and *In re Oda*, it is clear that the skilled practitioner would have no way of recognizing the error from the specification and claims alone. From the originally filed specification, there is no reason to presume that the sequence endpoints of the soluble domain and transmembrane domain would be anything other than what was originally recited. It would only be by using information outside of the specification, information that is new matter, that one could determine that these endpoints might differ. For the second factor, even if the practitioner recognized that the sequence description was flawed in some way, without outside information, the skilled practitioner would not be able to recognize the appropriate correction. Consequently, the error made in this application is not an obvious error, and the change which Applicant makes in the current claim set changes “the invention” in a way that the Court in *In re Oda* indicated would be a problem.

As set forth in the prior Office action, the original sequence listing for parent application PCT/US95/06386 numbered SEQ ID NO: 2 using negative numbers for the signal sequence (-45 through -1) and parent applications 08/930,564 and 09/227,853 (now U.S. Patent Nos. 6,410,506 and 6,642,006, respectively) altered the numbering of SEQ ID NO: 2 to remove the negative numbering and to begin numbering of SEQ ID NO: 2 at +1. This change was made in a substitute or amended sequence listing. The text of PCT/US95/06386 on page 6 is the same as that of the originally filed instant specification. PCT/US95/06386 does not refer to the negative numbering of SEQ ID NO: 2. The positions disclosed in PCT/US95/06386 on page 6 are considered to reflect the sequence disclosed in SEQ ID NO: 2 numbering from +1 at the first position rather than -45. This would have been a fair interpretation of the PCT/US95/06386 specification when read by one of ordinary skill in the art at the time of the invention. Thus, it reflects the present sequence listing for SEQ ID NO: 2 which explicitly numbers from +1 at the first position and does not provide basis for the altered ranges disclosed by applicant.

SEQ ID NO: 2 in PCT/US95/06385 used negative numbering for the signal sequence but the paragraph in question on page 5 of the specification did not. The total size of the protein in SEQ ID NO: 2 of PCT/US95/06386 was not 329 amino acids. It was 374 amino acids.

Example 2 discusses nucleotide ranges with respect to SEQ ID NO: 1. The text indicates that particular ranges of SEQ ID NO: 1 include or exclude certain domains but does not identify any end points by either nucleotide or amino acid. Note that the instant specification on page 29 indicates that the putative soluble portion of the polypeptide corresponds to nucleotides 1100-1248 of SEQ ID NO: 1. The disclosure makes no mention of the primers with respect to the sequence of Figure 1 and the numbering of SEQ ID NO: 1 has not changed when the disclosure

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of PCT/US95/05386 and the instant application are compared. According to applicant's arguments with respect to Example 2, nucleotide 1248 is the last nucleotide of the soluble portion. This nucleotide is in the middle of the codon for the amino acid Tyr at position 309 of SEQ ID NO: 2. At the very least it is unclear whether this page indicates that amino acid 309 is included or excluded from the soluble portion. Applicant's response does not address this portion of the rejection. Applicant's proposed correction also requires one to accept that the nucleotide range in Example 2 is correct and the original disclosure on page 5 is incorrect. Applicant's arguments require one to add +45 to certain (but not all) amino acid regions on page 5 to make the regions consistent. Applicant's arguments require one to arbitrarily decide which parts of the disclosure are in error and which are correct. This is not the standard for an obvious error with an obvious correction. It is further noted that the primers disclosed in Example 1 for the soluble form do not appear to correspond to the stated amino acid positions. Applicant's response does not address this portion of the rejection.

Inconsistencies cannot be characterized or corrected as obvious typographical errors unless the correction to the obvious typographical error is also clear. The originally filed specification does not make clear that the changes made by applicant are the obvious correction to any inconsistency.

Again, review of parent application (US 6,642,006 and US 6,410,506) with respect to these points reveals that no similar amendments appear to have been proposed and no declaration evidence or other arguments appear to have been presented. The sequence listing of the instant application was transferred from the parent application. The instant drawings also correspond to those in the parent applications.

Finally, review of parent application 09/227,853 reveals that the utility of the protein of SEQ ID NO: 2 was established based on a later published reference to Horie et al. (Genomics, 67:146-152, 2000). Horie et al. discloses and characterizes a protein identical to SEQ ID NO: 2. However, Figure 1C shows completely different amino acid ranges for the signal peptide, transmembrane region and so forth when compared to those originally disclosed in the instant application or the correction proposed by applicant. Applicant has not responded to this portion of the rejection.

Applicant is required to cancel the new matter in the reply to this Office Action.

### ***Claim Rejections - 35 USC § 112***

Claims 25 and 31-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter and written description rejection.

Claim 25 has been amended to be directed to a method for the treatment of a patient having need to inhibit TGF $\alpha$ -HII comprising administering an antibody that inhibits TGF $\alpha$ -HII and is capable of binding to a polypeptide comprising a member selected from the group consisting of amino acid ranges 1-374, 46-374, 1-309, 46-309, and 260-309 of SEQ ID NO: 2 as well as fragments thereof (see parts (g)-(i)).

Basis is not seen for the claimed methods. This rejection is maintained for reasons of record and as summarized below.



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The limitation that “an antibody that inhibits TGF $\alpha$ -HII” is not synonymous with the disclosure pointed to on page 24 that the antibodies **bind to and inactivate** TGF $\alpha$ -HII.

Applicant’s response does not address this portion of the rejection.

Original claims 19, 21-22, and 25 are reproduced below.

19. A polypeptide comprising a member selected from the group consisting of:

- (a) amino acids 1 to 374 of SEQ ID NO:2;
  - (b) amino acids 46 to 374 of SEQ ID NO:2;
  - (c) amino acids 1 to 264 of SEQ ID NO:2;
  - (d) amino acids 46 to 264 of SEQ ID NO:2;
  - (e) amino acids 215 to 264 of SEQ ID NO:2;
  - (f) a polypeptide encoded by the the cDNA contained in ATCC Deposit No. 97160;
  - (g) at least 30 contiguous amino acids of SEQ NO ID:2;
  - (h) at least 50 contiguous amino acids of SEQ NO ID:2;
  - (i) a polypeptide which is at least 70% identical to the polypeptide of (a), (b), (c), (d), (e), or (f);
- and
- (j) a polypeptide fragment of the polypeptide of (a), (b), (c), (d), (e), or(f).

21. An antibody against the polypeptide of claim 19.

22. A compound which inhibits activation of the polypeptide of claim 19.

25. A method for the treatment of a patient having need to inhibit TGF $\alpha$ -HII comprising:  
administering to the patient a therapeutically effective amount of the compound of claim 22.

As set forth in the prior Office actions, original claim 25 was not directed to administering an antibody. It was directed to administering a compound which inhibits activation of the polypeptide of claim 19. It was not directed to administering antibodies against the various polypeptides of claim 19. Applicant's response does not address this portion of the rejection.

In addition, the changes in amino acid ranges between original claim 19 and present claim 25 are still considered to be new matter for reasons of record and as discussed herein. Applicant's amendment to page 5 of the specification does not provide basis for changing the amino acid ranges to those now recited in instant claim 25 as based on original claim 19. The concepts recited in original claims 19 and 25 did not find support in original page 5.

The specification filed on 8/21/2003 was not a copy of the parent application. It was an amended specification as discussed in the preliminary amendment submitted on 10/20/2003. Paragraph [0025] on page 4 implies that only the mature sequence is present in ATCC deposit number 97160. Applicant asserted in the prosecution of parent application 09/227,853 that DNA encoding the full-length sequence of SEQ ID NO: 2 is present in the recited deposit.

Again, the specification has been amended to change the date of deposit of ATCC 97160 from 15 May 1995 to 24 May 1995. Applicant has altered the originally filed specification at pages 4, 28, 29, and 32 with respect to deposit information **without supplying the supporting**

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**documentation** from parent application 09/227,853. It is permissible to amend the specification to include post-filing date deposit information with a corroborating statement (see MPEP 2406.02) establishing that the biological material disclosed in the specification was in fact the material deposited at the later date. **Applicant must supply copies of the same evidence presented in 09/227,853 to complete the instant application.** These changes are considered to be new matter in the absence of this evidence. **A copy of the ATCC deposit slip is not sufficient.** The Jian Ni Declaration under 1.132 was submitted 9/7/00 to support the insertion of this deposit information.

Again, because claims 25 and 36 recite ATCC 97160, this deposit is required for enablement of these claims. Applicant is reminded that the Patent Office accepts Budapest approved deposits, as long as assurance is provided that the deposited materials will be made irrevocably available with no restrictions upon issuance of a patent. These criteria have not been met in the instant application. Applicant's response does not address this portion of the response.

Claims 25 and 31-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

This rejection is maintained for reasons of record.

Applicant argues particular conditions that are disclosed in the specification as being suitable for treatment with the recited antibodies. These conditions are not limitations of the claims and the claims embrace many other unidentified conditions.

The specification fails to identify any antibodies that bind to any portion of SEQ ID NO: 2 that are capable of inhibiting TGF $\alpha$ -HII either in vitro or in vivo. The specification and prior art of record fail to provide any evidence that there is a correlation between any in vitro antibody binding and any in vivo inhibition of TGF $\alpha$ -HII for any therapeutic purpose.

The specification fails to identify any fragments of SEQ ID NO:2 (including any 30 and 50 contiguous amino acid ranges) that could be used to generate antibodies that have the property of in vivo inhibition of TGF $\alpha$ -HII for any therapeutic purpose.

General teachings on antibody production are insufficient.

*In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

The claims are broad, the amount of direction or guidance presented is limited, and there are no working examples of any antibodies nor any examples of administering antibodies for any purpose in vivo or in vitro. As such, one of ordinary skill in the art would have been required to engage in extensive experimentation to produce antibodies appropriate for the claimed method of treatment. While those of ordinary skill in the art knew how to produce antibodies generally,

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there is no guidance or predictability with respect to those antibodies or epitopes likely to provide operable embodiments.

Note that while the specification produces the full-length protein recombinantly, no biological activity is established for the full-length protein or any of the fragments thereof. As such, **there is no guidance on how to assay for antibodies inhibiting TGF $\alpha$ -HII activity.**

Applicant has not responded to this portion of the rejection.

In the absence of such guidance or direction, it would constitute undue experimentation to practice the invention as claimed.

### ***Conclusion***

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

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1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712.

The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/  
Primary Examiner, Art Unit 1647

mpa